BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.33 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Annual Effective Policy Date: April 1, 2026

Original Policy Date: December 2011

Related Policies:

2.04.111 - Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management

Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Description

Description

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating between which men should undergo prostate biopsy and which rebiopsy after a prior negative biopsy. This evidence review addresses these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in evidence review 2.04.111.

OBJECTIVE

The objective of this evidence review is to determine whether testing for genetic and protein prostate biomarkers improves the net health outcome in men for whom an initial prostate biopsy or a repeat prostate biopsy is being considered.

POLICY STATEMENT

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered **investigational**:

- Kallikrein markers (eg, 4Kscore Test)
- Prostate Health Index (PHI)
- *HOXC6* and *DLX1* testing (eg, SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore)
- Autoantibodies ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifiny)
- *PCA3* testing (eg, Progensa PCA3 Assay)
- *TMPRSS:ERG* fusion genes (eg, MyProstate Score)
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- PanGIA Prostate
- MiCheck Prostate
- Candidate gene panels.

PCA3 testing (eg, Progensa PCA3 Assay),Prostate Health Index (phi),PCA3, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore) for cancer risk assessment of prostate cancer is considered **not medically necessary.**

Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered **investigational**.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (PHI™), MiCheck Prostate (Minomic Inc.), and ExoDx Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the Progensa PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (PHI ; Beckman Coulter) was approved by the FDA through the premarket approval process. The PHI test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

RATIONALE

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score, and PanGIA Prostate), the evidence includes systematic reviews, meta-analyses, and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The evidence supporting clinical utility varies by the test but has not been directly shown for any biomarker test. Absent direct evidence of clinical utility, a chain of evidence might be constructed. However, the performance of biomarker testing for directing biopsy referrals is uncertain. While some studies have shown a reduction or delay in biopsy based on testing, a chain of evidence for clinical utility cannot be constructed due to limitations in clinical validity. Test validation populations have included men with a positive digital rectal exam (DRE), a prostate-specific antigen (PSA) level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information from test results are less likely to be informative. Many biomarker tests do not have standardized cutoffs to recommend a biopsy. In addition, comparative studies of the many biomarkers are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The performance of biomarker testing for guiding rebiopsy decisions is lacking. The tests are associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies on clinical validity are limited and do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy, The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association et al

In 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published updated guidelines on the early detection of prostate cancer. Specific guidance related to diagnosis, risk assessment, and utilization of biomarkers are stated in Table 1 below. [73,]

Table 1. Relevant AUA/SUO Guideline Statements on Prostate Cancer Screening and Biopsy

Guideline Statement	Evidence Grade and Strength
When screening for prostate cancer, clinicians should use PSA as the first screening test	Strong Recommendation; Evidence Level: Grade A
For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy	Expert Opinion
Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer	Conditional Recommendation; Evidence Level: Grade C
For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy	Strong Recommendation; Evidence Level: Grade B
Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy.	Conditional Recommendation; Evidence Level: Grade C
After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy	Strong Recommendation; Evidence Level: Grade B
After a negative biopsy, clinicians may use blood-, urine-, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient"s management	Conditional Recommendation; Evidence Level: Grade C
In patients with multifocal HGPIN [high-grade prostatic intraepithelial neoplasia], clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings	Expert Opinion

DRE: digital rectal exam; PSA: prostate-specific antigen; mpMRI: multi-parametric magnetic resonance imaging

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer early detection (v.2.2024) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and DRE (category 2A evidence).[74,]

The NCCN guidelines state that "biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk". The guidelines recommend that the probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of the Prostate Health Index (PHI), SelectMDx, 4K score, ExoDx Prostate Test , MyProstate Score (MPS), and IsoPSA. NCCN also noted that the extent of validation of these tests across diverse populations is variable and is not yet known how these tests could be applied in optimal combination with magnetic resonance imaging (MRI).

For men who had a negative biopsy but are thought to be at higher risk, NCCN recommends to consider biomarkers that improve the specificity of screening (category 2A evidence). Tests that should be considered in the post-biopsy setting include percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA.

National Institute for Health and Care Excellence

In 2019 and in 2021, when guidelines were updated, the NICE guidelines did not recommend the Progensa PCA3 Assay or the PHI test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy. [75,]

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force** (2018) updated recommendations for prostate cancer screening. Genetic and protein biomarkers addressed in this evidence review, including *PCA3*, were not mentioned. [76,]

The U**.S. Preventive Services Task Force** advises individualized decision making about screening for prostate cancer after discussion with a clinician for men ages 55 to 69 (C recommendation) and recommends against PSA-based screening in men 70 and older (D recommendation). An update of these recommendations is pending.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017.
2. Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer. Feb 10 2009; 4 Suppl 1(Suppl 1): S2. PMID 19208207
3. Bell KJ, Del Mar C, Wright G, et al. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. Oct 01 2015; 137(7): 1749-57. PMID 25821151
4. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. Mar 1966; 50(3): 125-8. PMID 5948714
5. National Cancer Institute. SEER Database. https://seer.cancer.gov/seerinquiry/index.php?page=view&id=20170036&type=q. Accessed September 25, 2025.
6. Hoogendam A, Buntinx F, de Vet HC. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. Fam Pract. Dec 1999; 16(6): 621-6. PMID 10625141
7. Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol. Sep 2008; 54(3): 581-8. PMID 18423977
8. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level or =4.0 ng per milliliter. N Engl J Med. May 27 2004; 350(22): 2239-46. PMID 15163773
9. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. Apr 25 1991; 324(17): 1156-61. PMID 1707140
10. Aus G, Bergdahl S, Lodding P, et al. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol. Mar 2007; 51(3): 659-64. PMID 16934392
11. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol. Nov 2015; 68(5): 885-90. PMID 25791513
12. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Gteborg randomized population-based prostate cancer screening trial. Eur Urol. Sep 2015; 68(3): 354-60. PMID 25556937
13. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Gteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. Aug 2010; 11(8): 725-32. PMID 20598634
14. Schrder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. Mar 26 2009; 360(13): 1320-8. PMID 19297566
15. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010; 60(2): 70-98. PMID 20200110
16. Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. Jan 09 2012; 344: d7894. PMID 22232535
17. Lavalle LT, Binette A, Witiuk K, et al. Reducing the Harm of Prostate Cancer Screening: Repeated Prostate-Specific Antigen Testing. Mayo Clin Proc. Jan 2016; 91(1): 17-22. PMID 26688045
18. Ruiz-Aragn J, Mrquez-Pelez S. [Assessment of the PCA3 test for prostate cancer diagnosis: a systematic review and meta-analysis]. Actas Urol Esp. Apr 2010; 34(4): 346-55. PMID 20470697

19. Mackinnon AC, Yan BC, Joseph LJ, et al. Molecular biology underlying the clinical heterogeneity of prostate cancer: an update. Arch Pathol Lab Med. Jul 2009; 133(7): 1033-40. PMID 19642730
20. Partin AW, Brawer MK, Subong EN, et al. Prospective evaluation of percent free-PSA and complexed-PSA for early detection of prostate cancer. Prostate Cancer Prostatic Dis. Jun 1998; 1(4): 197-203. PMID 12496895
21. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst. Apr 19 2006; 98(8): 529-34. PMID 16622122
22. van Vugt HA, Roobol MJ, Kranse R, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. Eur J Cancer. Apr 2011; 47(6): 903-9. PMID 21163642
23. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol. Dec 2016; 196(6): 1613-1618. PMID 27320841
24. Mi C, Bai L, Yang Y, et al. 4Kscore diagnostic value in patients with high-grade prostate cancer using cutoff values of 7.5% to 10%: A meta-analysis. Urol Oncol. Jun 2021; 39(6): 366.e1-366.e10. PMID 33685800
25. Kawada T, Shim SR, Quhal F, et al. Diagnostic Accuracy of Liquid Biomarkers for Clinically Significant Prostate Cancer Detection: A Systematic Review and Diagnostic Meta-analysis of Multiple Thresholds. Eur Urol Oncol. Aug 2024; 7(4): 649-662. PMID 37981495
26. Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-Kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. Clin Genitourin Cancer. Aug 2017; 15(4): 429-439.e1. PMID 28111174
27. Bhattu AS, Zappala SM, Parekh DJ, et al. A 4Kscore Cut-off of 7.5% for Prostate Biopsy Decisions Provides High Sensitivity and Negative Predictive Value for Significant Prostate Cancer. Urology. Feb 2021; 148: 53-58. PMID 33217456
28. Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the Specificity of Screening for Lethal Prostate Cancer Using Prostate-specific Antigen and a Panel of Kallikrein Markers: A Nested Case-Control Study. Eur Urol. Aug 2015; 68(2): 207-13. PMID 25682340
29. Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int. Jul 2017; 120(1): 61-68. PMID 27743489
30. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol. Sep 2015; 68(3): 464-70. PMID 25454615
31. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. Rev Urol. 2015; 17(4): 231-40. PMID 26839521
32. Pecoraro V, Roli L, Plebani M, et al. Clinical utility of the (-2)proPSA and evaluation of the evidence: a systematic review. Clin Chem Lab Med. Jul 01 2016; 54(7): 1123-32. PMID 26609863
33. Anyango R, Ojwando J, Mwita C, et al. Diagnostic accuracy of [-2]proPSA versus Gleason score and Prostate Health Index versus Gleason score for the determination of aggressive prostate cancer: a systematic review. JBI Evid Synth. Jun 2021; 19(6): 1263-1291. PMID 33741840
34. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol. May 2011; 185(5): 1650-5. PMID 21419439
35. Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. Prostate Cancer Prostatic Dis. Jun 2017; 20(2): 228-233. PMID 28117387
36. White J, Shenoy BV, Tutrone RF, et al. Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting. Prostate Cancer Prostatic Dis. Apr 2018; 21(1): 78-84. PMID 29158509
37. Sanda MG, Feng Z, Howard DH, et al. Association Between Combined TMPRSS2:ERG and PCA3 RNA Urinary Testing and Detection of Aggressive Prostate Cancer. JAMA Oncol. Aug 01 2017; 3(8): 1085-1093. PMID 28520829
38. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. Eur Urol. Jul 2016; 70(1): 45-53. PMID 25985884
39. Ankerst DP, Goros M, Tomlins SA, et al. Incorporation of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG into Prostate Cancer Prevention Trial Risk Calculator. Eur Urol Focus. Jan 2019; 5(1): 54-61. PMID 29422418
40. Tosoian JJ, Trock BJ, Morgan TM, et al. Use of the MyProstateScore Test to Rule Out Clinically Significant Cancer: Validation of a Straightforward Clinical Testing Approach. J Urol. Mar 2021; 205(3): 732-739. PMID 33080150
41. Newcomb LF, Zheng Y, Faino AV, et al. Performance of PCA3 and TMPRSS2:ERG urinary biomarkers in prediction of biopsy outcome in the Canary Prostate Active Surveillance Study (PASS). Prostate Cancer Prostatic Dis. Sep 2019; 22(3): 438-445. PMID 30664734
42. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol. Nov 2016; 70(5): 740-748. PMID 27108162
43. McKiernan J, Donovan MJ, O'Neill V, et al. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. JAMA Oncol. Jul 01 2016; 2(7): 882-9. PMID 27032035
44. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. Prostate Cancer Prostatic Dis. Dec 2020; 23(4): 607-614. PMID 32382078
45. Tutrone R, Lowentritt B, Neuman B, et al. ExoDx prostate test as a predictor of outcomes of high-grade prostate cancer - an interim analysis. Prostate Cancer Prostatic Dis. Sep 2023; 26(3): 596-601. PMID 37193776
46. Schipper M, Wang G, Giles N, et al. Novel prostate cancer biomarkers derived from autoantibody signatures. Transl Oncol. Apr 2015; 8(2): 106-11. PMID 25926076
47. Shore ND, Pieczonka CM, Henderson RJ, et al. Development and evaluation of the MiCheck test for aggressive prostate cancer. Urol Oncol. Aug 2020; 38(8): 683.e11-683.e18. PMID 32305266
48. Gillatt D, Polikarpov D, Smith I, Lau H, Kim L, Huynh CC, et al. MP17-07VALIDATION OF MICHECK PROSTATE FOR SIGNIFICANT PROSTATE CANCER IN AN AUSTRALIAN POPULATION. Journal of Urology [Internet]. 2023 Apr 1; 209(Supplement 4):e215.

49. Wysock JS, Becher E, Persily J, et al. Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. Urology. Jul 2020; 141: 119-124. PMID 32294481
50. Cui Y, Cao W, Li Q, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. Sci Rep. May 10 2016; 6: 25776. PMID 27161545
51. Rodrguez SVM, Garca-Perdomo HA. Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis. Can Urol Assoc J. May 2020; 14(5): E214-E219. PMID 31793864
52. Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technol Assess. Oct 2015; 19(87): i-xxxi, 1-191. PMID 26507078
53. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer?. J Clin Oncol. Dec 20 2014; 32(36): 4066-72. PMID 25385735
54. Hennenlotter J, Neumann T, Alperowitz S, et al. Age-Adapted Prostate Cancer Gene 3 Score Interpretation - Suggestions for Clinical Use. Clin Lab. Mar 01 2020; 66(3). PMID 32162868
55. Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. Cancer Epidemiol Biomarkers Prev. Feb 2011; 20(2): 255-61. PMID 21148123
56. Ruffion A, Devonec M, Champetier D, et al. PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy. Int J Mol Sci. Aug 29 2013; 14(9): 17767-80. PMID 23994838
57. Ruffion A, Perrin P, Devonec M, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. World J Urol. Aug 2014; 32(4): 917-23. PMID 24500192
58. Merdan S, Tomlins SA, Barnett CL, et al. Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy. Cancer. Nov 15 2015; 121(22): 4071-9. PMID 26280815
59. Djavan B, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol. Sep 2001; 166(3): 856-60. PMID 11490233
60. Lujan M, Paez A, Santonja C, et al. Prostate cancer detection and tumor characteristics in men with multiple biopsy sessions. Prostate Cancer Prostatic Dis. 2004; 7(3): 238-42. PMID 15289810
61. Stewart GD, Van Neste L, Delvenne P, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. J Urol. Mar 2013; 189(3): 1110-6. PMID 22999998
62. Partin AW, Van Neste L, Klein EA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. J Urol. Oct 2014; 192(4): 1081-7. PMID 24747657
63. Waterhouse RL, Van Neste L, Moses KA, et al. Evaluation of an Epigenetic Assay for Predicting Repeat Prostate Biopsy Outcome in African American Men. Urology. Jun 2019; 128: 62-65. PMID 29660369
64. Van Neste L, Partin AW, Stewart GD, et al. Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies. Prostate. Sep 2016; 76(12): 1078-87. PMID 27121847
65. Partin AW, VAN Criekinge W, Trock BJ, et al. CLINICAL EVALUATION OF AN EPIGENETIC ASSAY TO PREDICT MISSED CANCER IN PROSTATE BIOPSY SPECIMENS. Trans Am Clin Climatol Assoc. 2016; 127: 313-327. PMID 28066067
66. Food and Drug Administration. Summary of Safety and Effectiveness Data. PMA P090026. Quantitative test for determination of [-2]proPSA levels. Silver Spring, MD: Food and Drug Administration; 2012.
67. Aubry W, Lieberthal R, Willis A, et al. Budget impact model: epigenetic assay can help avoid unnecessary repeated prostate biopsies and reduce healthcare spending. Am Health Drug Benefits. Jan 2013; 6(1): 15-24. PMID 24991343
68. Robinson K, Creed J, Reguly B, et al. Accurate prediction of repeat prostate biopsy outcomes by a mitochondrial DNA deletion assay. Prostate Cancer Prostatic Dis. Jun 2010; 13(2): 126-31. PMID 20084081
69. Legisi L, DeSa E, Qureshi MN. Use of the Prostate Core Mitomic Test in Repeated Biopsy Decision-Making: Real-World Assessment of Clinical Utility in a Multicenter Patient Population. Am Health Drug Benefits. Dec 2016; 9(9): 497-502. PMID 28465777
70. Leyten GH, Hessels D, Smit FP, et al. Identification of a Candidate Gene Panel for the Early Diagnosis of Prostate Cancer. Clin Cancer Res. Jul 01 2015; 21(13): 3061-70. PMID 25788493
71. Xiao K, Guo J, Zhang X, et al. Use of two gene panels for prostate cancer diagnosis and patient risk stratification. Tumour Biol. Aug 2016; 37(8): 10115-22. PMID 26820133
72. Tosoian JJ, Sessine MS, Trock BJ, et al. MyProstateScore in men considering repeat biopsy: validation of a simple testing approach. Prostate Cancer Prostatic Dis. Sep 2023; 26(3): 563-567. PMID 36585434
73. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part I: Prostate Cancer Screening. J Urol. Jul 2023; 210(1): 46-53. PMID 37096582
74. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer early detection V.2.2025. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Accessed September 25, 2025.
75. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [NG131]. 2019. Updated December 15, 2021; https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#assessment-and-diagnosis. Accessed September 25, 2025.
76. U. S. Preventive Services Task Force. Prostate Cancer: Screening. 2018; https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/prostate-cancer-screening-adults. Accessed September 25, 2025.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
June 2013	Replace policy	Policy updated with literature review, references added, policy statement changed PCA3 from investigational to not medically necessary.
June 2014	Replace policy	Policy updated with literature review through March 16, 2014; references 1, 12-13, 31-46, 60-65, 67-70, 82-88 added. No change to policy statement.
June 2015	Replace policy	Policy updated with literature review through March 16, 2015. Policy revised to focus on diagnostic testing (as well as SNP testing for cancer risk assessment). Policy statements revised to include an expanded list of diagnostic genetic and protein biomarker tests as investigational. Prognostic testing is being moved to Policy No. 2.04.111. References extensively revised. Title changed "Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer.,
December 2016	Replace policy	Policy updated with literature review through August 26, 2016; references 1-28, 31-44, 46-57, 60-65, 82, 96-99, 102, 104, 107, 110-111, and 117-118 added. Prostate Health Index (phi) biomarker test added to review and policy statement.
March 2018	Replace policy	Policy updated with literature review through July 26, 2017; references 1-2 and 22 updated; reference 1, 22, and 27 added; Prostarix test removed from policy and policy statement; policy statement corrected due to FDA premarket approval status to change PCA3 and Prostate Health Index (phi) biomarker tests from investigational to not medically necessary, otherwise policy statement unchanged.
March 2019	Replace policy	Policy updated with literature review through September 4, 2018; references 6, 32-34, 36-38, 45, 50, 55, and 60 added. The SelectMDx, ExoDx Prostate (IntelliScore), and Apifiny tests added as investigational.
March 2020	Replace policy	Policy updated with literature review through September 18, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 16, 2020; references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through February 19, 2021. PanGIA Prostate added as investigational.
March 2022	Replace policy	Policy updated with literature review through October 6, 2021; references added. MyProstateScore (renamed from MiPS) added as an example of a TMPRSS:ERG fusion gene test.Policy statements otherwise unchanged.
March 2023	Replace policy	Policy updated with literature review through September 19, 2022; references added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through September 26, 2023; references added. Policy statements unchanged.
March 2025	Replace policy	Policy updated with literature review through September 16, 2024; references added. Policy statements unchanged.
March 2026	Replace policy	Policy updated with literature review through September 25, 2025; References added. Added MiCheck prostate test. Policy statements unchanged.